L2: Entry 60 of 62 File: USPT Jan 13, 1976

DOCUMENT-IDENTIFIER: US 3932498 A
TITLE: 3-Indenyl-.gamma.-(ketobutyric)-acid compounds

BSPR:
In the preparation of the compounds of the instant invention, again a number of routes are possible, as shown in Flow Sheet II. The first step in ring closure of the .alpha.-aryl propionic acid to form an indanone which may be carried out by a Friedel-Crafts Reaction using a Lewis acid catalyst or by heating with polyphosphoric acid. The indanone may be condensed with an .alpha.-halo ester in the Reformatsky Reaction to introduce an aliphatic acid side chain by replacing the carbonyl group. Alternatively, this introduction can be carried out by use of a Wittig Reaction in which the reagent is an .alpha.-triphenylphosphinyl ester, a reagent which replaces the carbonyl with a double bond to a carbon. This is immediately rearranged into the indene. If the Reformatsky Reaction route is used, the intermediate 3-hydroxy-3aliphatic acid derivative must be dehydrated to the indene. In the preparation of the .alpha.-(.beta.-hydroxybutyric) acid compounds, the indenyl-3-acetic acid ester is reduced to the corresponding alcohol, which in turn is oxidized to the alcohol compound. This latter compound is then treated with a halo acetic ester to form the .alpha.-(.beta.-hydroxybutyric) acid ester. The corresponding .alpha.-(.beta.-ketobutyric) acid ester is prepared by oxidation of the .alpha.-(.beta.-hydroxybutyric) acid ester. The indenyl-3-.alpha.-(.alpha.-ketobutyric) acid compound is prepared by condensation of the indanone with a 3-halo butyric acid ester and subsequent reaction of the acetylinic compound to form the .alpha.-ketobutyric acid compound. The indenyl-3-.alpha.-(.alpha.-hydroxybutyric) acid compound may be readily prepared by reduction of the corresponding indenyl-3-.alpha.-(.alpha.-ketobutyric) acid compound. The introduction of the 1-substituent is carried out in one of two ways. The first is the direct reaction of the indene with the aldehyde of the structural characteristics defined, using a strong base as a catalyst and warming, if necessary, to form the carbanion. The reaction can be carried out in a number of solvents such as polar solvents like dimethoxyethane, aqueous methanol, pyridine, liquid ammonia, dimethylformamide and the like, or even in non-polar solvents such as benzene, etc. Alternatively, an indanone can be brominated and then dehydrogen-brominated to an indenone and the indenone carbonyl replaced by the substituent using the .alpha.-triphenyl-phosphinyl compounds of the desired structure. Note that a loweralkyl ester of the desired compound is formed in the third step. This ester can then be hydrolyzed to give the free acids and oxidized to give the sulfoxides and sulfones from which the salts, other esters and the amides may be formed. The keto substituted acid side chains may be prepared by oxidizing the hydroxy acid side chain.

L2: Entry 30 of 62 File: USPT Apr 7, 1992

DOCUMENT-IDENTIFIER: US 5102893 A
TITLE: Trans-6-(2-(n-heteroaryl-3,5-disubstituted)pyrazol-4-yl)-ethyl- or ethenyl)tetrahydro-4-hydroxypyran-2-one inhibitors of cholesterol biosynthesis

DEPR:
For example, the 4-halopyrazole compounds (VII) are coupled with ethyl acrylate, employing the Heck reaction (cf. R. F. Heck, Org. Reac., 27, 345-390 (1982)). The esters (a) are reduced at -78.degree. C. by the action of diisobutyl aluminum hydride to yield the alcohols (b) which are then oxidized to the corresponding aldehydes (c) with manganese dioxide. Aldol condensation of the aldehydes (c) with the sodium lithium dianion of ethyl acetoacetate at -78.degree. C. in tetrahydrofuran (cf. Kraus et al, J. Org. Chem., 48, 2111 (1983)) gives the .delta.-hydroxy-.beta.-keto esters (d). The products of this condensation are then reduced in a sequence of steps in which they are first dissolved in a polar solvent such as tetrahydrofuran under dry air atmosphere. A small excess of triethyl borane and catalytic amounts of pivalic acid (2,2-dimethylpropanoic acid) are next added. The mixtures are stirred at room temperature for a short period, then cooled to -78.degree. C.; dry methanol is added followed by sodium borohydride. The mixtures are kept at -78.degree. C. for 6 hours before treating with ice cold hydrogen peroxide. The substituted 3,5-dihydroxy-6-heptenoic acid ethyl esters (IX) are isolated having the preferred R*S* configuration. The esters (IX) may be hydrolyzed to the sodium salts. The esters (IX) or the free acids produced by acidification of the sodium salts can be dehydrated to the lactones (X) by heating the acid in an inert solvent such as toluene with concomitant azeotropic removal of water.

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L3: Entry 6 of 8 File: USPT Jun 13, 1995

DOCUMENT-IDENTIFIER: US 5424444 A
TITLE: Method of preparing enantiomerically-pure 3-methyl-5-(1-alkyl-2(S)-pyrrolidinyl) isoxazoles

BSPV:
(a) reducing the CBZ-protected-L-proline of formula (9), ##STR21## with a suitable reducing agent to give the CBZ-protected-L-prolinol of formula (10), ##STR22## (b) selectively oxidizing the prolinol compound (10) to give the CBZ-protected-L-prolinal of formula (11), ##STR23## (c) condensing the compound (11) with an ylid derived from acetone to give the intermediate product of formula (12), ##STR24## (d) converting the ketone compound (12) into its oxime by reaction with hydroxylamine in the presence of a weak organic base and a suitable solvent to give the compound (13), ##STR25## (e) cyclizing and dehydrating compound (13) by reaction with Kl and I.sub.2 in the presence of a weak organic base to give the protected intermediate compound (14), ##STR26## and (f) reductively cleaving the protecting group by reaction with a suitable hydride reducing agent and isolating the desired product, 3-methyl-5-(1-methyl-2-pyrrolidinyl)isoxazole, in high chiral purity.

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